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4,4′-Methylenebis(2-chloroaniline) (MOCA) – Evaluation of a BAR

Assessment Values in Biological Material – Translation of the German version from 2013

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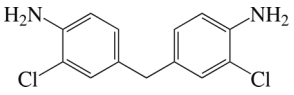
4,4′-methylenebis(2-chloroaniline), MOCA, BAR, biological reference value, biomonitoring

BAR (2012)	**< 1 mg 4,4′-methylenebis(2-chloroaniline) (MOCA) (after hydrolysis)/l urine** Sampling time: end of exposure or end of shift
MAK value	**not established**
Absorption through the skin (1993)	H
Carcinogenicity (1993)	Category 2
Synonyms	4,4′-Diamino-3,3′-dichlorodiphenylmethane 3,3′-Dichloro-4,4′-diaminodiphenylmethane 2,2′-Dichloro-4,4′-methylenedianiline Bis(4-amino-3-chlorophenyl)methane Bis(3-chloro-4-aminophenyl)methane Methylenebis(3-chloro-4-aminobenzene) 4,4′-Methylenebis(ortho-chloroaniline) MOCA MBOCA
CAS number	101-14-4
Formula	 $C_{13}H_{12}Cl_2N_2$
Molar mass	267.15 g/mol
Melting point	110 °C
Boiling point	202–214 °C (0.3 mm Hg)
Vapour pressure at 20 °C	4.93293×10^{-6} hPa
Density at 20 °C	1.44 g/cm³

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4,4′-Methylenebis(2-chloroaniline) (MOCA) does not naturally occur in the environment. It is mainly used as a crosslinker for polyurethane prepolymers in the manufacture of specialised, pourable urethane rubber products. The moulded parts are used in industry for example in the form of rollers, shock-absorption pads or conveyor belts. In Asia, MOCA is used as hardener for roof coatings and in wood surface coating materials (IARC 2010).

1 Metabolism and Toxicokinetics

The literature on the metabolism and toxicokinetics of MOCA is compiled in the occupational-medical and toxicological documentation of the maximum workplace concentration (MAK value) (Greim 1996) and in the monographs of the IARC (1993, 2010).

MOCA is absorbed both via the airways and through the skin. It was designated with an "H", as it is readily absorbed through the intact skin, this being the main uptake route at the workplace (Greim 1996).

MOCA is mainly metabolised to the N-glucuronide and to a lesser extent to N-acetyl-MOCA and N,N′-diacetyl-MOCA. In urine, it is excreted in the form of free MOCA or as a conjugate, where N-glucuronide conjugate levels found in the urine of occupationally exposed workers were 2 to 3 times higher than those of free MOCA (Cocker et al. 1990). The levels of N-acetyl-MOCA and N,N′-diacetyl-MOCA found in the urine of exposed persons are mostly 10% below those of free MOCA (Ducos et al. 1985; Shih et al. 2007). It seems that urinary concentrations of N,N′-diacetyl-MOCA higher than 1 µg/l are found only in exceptional cases (Ducos et al. 1985). After an acute dermal exposure, the peak level of urinary MOCA excretion was determined 4 hours after the exposure; the half-life was 23 hours (Osorio et al. 1990).

Metabolites formed by N-oxidation of MOCA bind covalently to macromolecules such as DNA, haemoglobin and other proteins. This has been demonstrated by several studies in rats and dogs (Greim 1996; IARC 1993, 2010); in addition, in exposed persons, DNA adducts have been found in urothelial cells (Kaderlik et al. 1993) and haemoglobin adducts in blood (Vaughan and Kenyon 1996).

2 Critical Toxicity

As, in occupationally exposed persons, hardly any symptoms have been described, it appears that the acute toxicity of MOCA in humans is low. In two accidents at work involving liquid MOCA described in the literature, the affected persons reported burning in or on the sprayed body parts (eyes, face, arms, upper body and legs). In the first case conjunctivitis was diagnosed. Swallowing of the substance led to nausea. Urinalyses indicated rapid excretion of MOCA (Greim 1996). As sign of acute toxicity, the formation of methaemoglobin, spleen toxicity and fibrosation of the spleen, liver and kidneys have been described in rodents. The effects are similar to those found with o-toluidine and 4-chloro-o-toluidine, which is indicative of a common mode of action (IARC 2010).

In 1993, MOCA was classified by the Commission in Carcinogen Category 2 (Greim 1996). In carcinogenicity studies in mice, rats and dogs, MOCA caused tumours in the lungs, liver, mammary and Zymbal glands, and in the urinary bladder. Numerous mutagenicity tests carried out in different systems also yielded positive results. Two cohort studies gave reason to suspect an increase in the risk of bladder carcinoma in humans. Since then, two more recent reports on individual cases of urothelial neoplasms in workers exposed to MOCA have become available (Chen et al. 2005; Liu et al. 2005).

The IARC (International Agency for Research on Cancer) and the SCOEL (Scientific Committee on Occupational Exposure Limits) classified MOCA in 2010 as a human carcinogen (IARC Group 1: Carcinogenic to humans (IARC 2010), SCOEL carcinogen group A: Non-threshold genotoxic carcinogens (SCOEL 2013)).

3 Exposure and Effects

3.1 Relationship between external and internal exposure

In a MOCA producing plant in the USA, Linch et al. (1971) investigated the correlation between the MOCA concentration in the air and in urine. In one work area, only 15% of the air samples were slightly above the detection limit, whereas urine concentrations of 40–3800 µg MOCA/l were obtained. No relationship between external and internal exposure could be determined.

Ichikawa et al. (1990) investigated the concentrations of MOCA in personal air samples and in the urine of five workers at a polyurethane elastomer plant. The urinary excretion of MOCA at the end of shift (mean: 2.4–96.6 µg/g creatinine) were markedly higher than expected from the air concentrations actually determined (mean: 0.2–8.9 µg/m^3).

Clapp et al. (1991) compared air, surface and skin exposure samples with biomonitoring results in workers at a polyurethane factory. The obtained personal air samples showed concentrations below 1 µg MOCA/m^3, in spite of concentrations of up to 92 µg/m^3 in the room air samples. The work surfaces were moderately contaminated with MOCA dust (up to 19 µg/100 cm^2). The average MOCA concentration found on skin pads worn on workers' hands was generally less than 10 µg/set. Sixty-six percent of the urine samples had detectable levels of MOCA, and the highest concentration measured was 159 µg/l. The urinary concentrations of MOCA correlated with the potential exposure of a worker as associated with the immediacy of his MOCA contact, the protective clothing used and the general task.

In one study, MOCA concentrations were determined in 20 polyurethane elastomer factories in Great Britain. In 84% of the personal air samples, the MOCA concentration was below the detection limit, the average concentration of the positive measurements was 3 µg/m^3. In the urine, MOCA was detected in 51% of the 78 samples. The average concentration was 6.6 µmol MOCA/mol creatinine (Cocker et al. 2009).

Altogether, the studies showed no correlation between external and internal exposure and indicated that a significant fraction of MOCA absorption takes place through the skin.

The literature on internal exposure to MOCA in workers in the production of MOCA and polyurethane is summarised in Table 1.

Tab. 1 Urinary levels of MOCA in MOCA and polyurethane production workers, according to IARC (2010)

Country, year of study	Task	n	Measurement	MOCA in urine		References
				[µg/l]	[µg/g creatinine]	
USA, 1969	MOCA production	216	mean	620		Linch et al. 1971
USA, 1970		213	mean	250		
Germany	plastics manufacturing and processing plant	49	range	< 15–100		Will et al. 1981
UK	polyurethane elastomer production					Thomas and Wilson 1984
1978	before improved hygiene measures	12–15	mean		5 µmol/mol	
1980	after improvements	12–15	mean		50 µmol/mol	

Tab. 1 *(continued)*

Country, year of study	Task	n	Measurement	MOCA in urine		References
				[µg/l]	[µg/g creatinine]	
France	MOCA production					Ducos et al. 1985
1982	before improved production process	12	mean	600	450	
1983	after improvements	11	mean	62	63	
France	polyurethane elastomer production					
1982	before improved production process	4	range	75–940	31–510	
1983	after improvements	3	range	4–9	3.5–8.9	
	17 other factories	no data	range	< DL–600	< DL–310	
			max	1600	1400	
USA, 1980–1983	MOCA production/processing, 54 companies	3323		16.9% > 50 9.2% > 100		Ward et al. 1987
Australia	polyurethane polymer production, 5 factories					Wan et al. 1989
1986	before training programme		GM	29.6		
1987	after training programme		GM	10.4		
Japan	polyurethane elastomer production workers	5	mean (range)		2.4–96.6	Ichikawa et al. 1990
USA, 1981	MOCA production	385	max	50 000		Ward et al. 1990
USA, 1986	manufacturing of polyurethane products	77		6.5% > 50		Clapp et al. 1991
	mixing	10	mean	61.9		
	injection moulding	35	mean	14.8		
USA	polyurethane production					Lowry and Clapp 1992
1985	33 companies	1228		12% > 50		
1990	38 companies	1441		8% > 50		
Australia	5 manufacturers of polyurethane elastomers		range	4.5–2390 nmol/l		Vaughan and Kenyon 1996
Australia, 1998	polyurethane production	12	range		0.4–48.6 µmol/mol	Murray and Edwards 1999
France	polyurethane manufacture workers (n = 40)	103	mean	55	35	Robert et al. 1999 b
	mixer (n = 6)	17	mean	135	56	
	moulder (n = 10)	26	mean	20	10	
	maintenance (n = 6)	17	mean	158	128	
	others (n = 13)	38	mean	7	6	
Taiwan, China, 2002	MOCA production	10	mean (range)		5544 (268–15 701)	Liu et al. 2005
USA	polyurethane manufacturing	1	–	15		Fairfax and Porter 2006
Taiwan, China	MOCA production, 3 factories	54	mean	191.9	248.3	Shih et al. 2007

Tab. 1 *(continued)*

Country, year of study	Task	n	Measurement	MOCA in urine		References
				[µg/l]	[µg/g creatinine]	
UK, 2005/2006	polyurethane elastomer manufacturing	78				Cocker et al. 2009
	weighing, casting, mixing		mean		3.2 µmol/mol	
	casting		mean		9.2 µmol/mol	
	demoulding		mean		8.3 µmol/mol	
	maintenance		mean		3.5 µmol/mol	
	all tasks		mean		7.2 µmol/mol	
	indirect exposure		mean		3.4 µmol/mol	
	total		mean		6.6 µmol/mol	

DL = detection limit; GM = geometric mean; max = maximum; n = number of samples

3.2 Relationship between internal exposure and effects

There are no relevant data available for internal exposure and effects.

4 Selection of Indicators

Most of the determinations of occupational exposure to MOCA are carried out by analysing free and conjugated MOCA (i.e. total MOCA after acid hydrolysis of the conjugates) in the post-shift urine. Because of the short elimination time the occupational exposure over the preceding 24 hours is thus recorded (Osorio et al. 1990). In some studies, the concentration of the metabolite N-acetyl-4,4′-methylenebis(2-chloroaniline) (acetyl-MOCA) in urine was additionally analysed (Cocker et al. 1988; Shih et al. 2007).

Alternatively, the concentration of the haemoglobin adducts of MOCA can be determined in blood, which is a better way of reflecting exposure over an extended period (lifespan of an erythrocyte, 120 days) than investigating the urinary excretion of MOCA (Vaughan and Kenyon 1996). However, there are only few data available for this parameter in exposed humans (Vaughan and Kenyon 1996), though data for the dose dependency of haemoglobin adducts have been obtained from animal studies (Bailey et al. 1993; Sabbioni and Schütze 1998). In addition, for estimating the point in time of a higher exposure more accurately the use of parallel determinations of MOCA concentrations in urine, blood and plasma has been discussed as a possibility (Vaughan and Kenyon 1996).

5 Analytical Methods

For the determination of MOCA in urine (total MOCA after acid hydrolysis of the conjugates) several analytical methods have been described: high-performance liquid chromatography (HPLC) (Cocker et al. 1996; Robert et al. 1999 a), liquid chromatography with tandem mass spectrometry (LC-MS/MS) (Shih et al. 2007) and gas chromatography coupled with mass spectrometry (GC-MS) (Cocker et al. 1988, 1990; Wu et al. 1996). The detection limit is at 1 µg MOCA (after hydrolysis)/l urine (Robert et al. 1999 a; Shih et al. 2007; Wu et al. 1996).

Vaughan and Kenyon (1996) have described methods for the determination of haemoglobin adducts using GC-MS and GC with electron capture detection (GC-ECD).

6 Background Exposure

MOCA is not a naturally occurring substance. Therefore, a detectable urinary excretion of MOCA is indicative of occupational exposure. In rare cases, through contamination of the living area (for example after an inadvertent release of MOCA into the environment), the consumption of vegetables from contaminated areas or by living in contact with family members subject to occupational exposure, a MOCA exposure of up to 15 µg/l urine can be found in the general population (IARC 2010).

7 Evaluation

In persons without occupational exposure, MOCA is generally not found with the detection limit of the applied methods of 1 µg MOCA (after hydrolysis)/l urine.

Therefore,

a BAR (biological reference value) of < 1 µg 4,4′-methylenebis(2-chloroaniline) (after hydrolysis)/l urine

is established.

Sampling time is at the end of exposure or end of shift.

On the basis of the studies available and because of the very good skin penetration of MOCA, no correlation between external and internal exposure is determinable, and thus the derivation of EKA not possible. As no data for internal exposure and effects of MOCA are available, no health-based BLW (biological guidance value) can be evaluated at present either.

At present, the ACGIH (American Conference of Governmental Industrial Hygienists) and the SCOEL (Scientific Committee on Occupational Exposure Limits) also regard the available data as being insufficient for the derivation of a biological exposure index (BEI) or of an occupational exposure limit (OEL) (ACGIH 2001; SCOEL 2013). However, the SCOEL proposes a biological guidance value (BGV) of 5 µmol total MOCA/mol creatinine (corresponding to 14 µg/l urine) (SCOEL 2013). In some countries, however, hygiene-based limit values have been derived: France (Robert et al. 1999 b, 2001), Western Australia (Wan et al. 1989), California (Cal/OSHA 2018), Japan (IARC 2010), Finland (FIOH 2008) and United Kingdom (Cocker et al. 2009).

The working group "Setting of Threshold Limit Values in Biological Materials" does not evaluate assessment values in biological materials based on hygienic considerations.

Because of lack of data, the derivation of a health-based threshold limit value is not possible at present.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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